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Methods for deformulating drugs

Chemical sciences

In this white paper we look at reverse engineering existing drug products using Raman imaging.

Background

The FDA has a number of regulatory routes through which a company can seek approval for a generic drug.

The most notable is the Abbreviated New Drug Application (ANDA) route whereby a generic company develops an exact copy of the innovator product and can use the safety and efficacy data from the innovator in their submission. This route was facilitated in the 1980s through the Drug Price Competition and Patent Term Restoration Act, informally known as the Hatch-Waxman Act after Senator Orrin Hatch and Representative Henry Waxman who sponsored it.

The US government at the time were concerned about the low number of generic drug approvals. Before the Hatch-Waxman act, innovator companies could easily create legal obstacles for companies looking to develop generic medicines; this made generic drug development an unattractive industry. The Hatch-Waxman Act removed many of these obstacles, successfully incentivising generics companies to produce affordable generic medicines, whilst simultaneously protecting innovator companies by allowing them a sufficient exclusivity period after the initial release of their drug and keep innovation profitable.

The alternative route for generic drug approvals is 505(b)(2). This route is for drug product submissions that may contain reports of safety and effectiveness investigations from previous studies performed on a chosen reference product, but the format of the drug is intentionally different to that of the reference product. Classic examples of 505(b)(2) candidates are the repurposing of existing drugs for new indications or reformulating existing drugs for a different delivery route. In these cases, drug makers can rely on the toxicity and safety data generated for the API by a marketed reference product, but will still be required to demonstrate efficacy and effectiveness of their formulation in the clinic.

When it comes to ANDAs, there is a growing interest in the field of biowaivers. A biowaiver is a regulatory pathway whereby a generic drug can be proven to be equivalent to the reference product through *in vitro* testing alone, without the need to undergo bioequivalence studies. In order to be considered for a biowaiver, a drug must exhibit Q1, Q2 and Q3 sameness.

Q1	Qualitative similarity: the test and reference products contain the same active and inactive ingredients.
Q2	Quantitative similarity of composition: the same amounts of active and inactive ingredients.
Q3	Structural sameness (currently reserved for topical medications): equivalent microstructure

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4365090/

In order to prove Q1 and Q2 equivalence in solid dosage forms, formulators need to prove that the generic product contains the same components in the same concentrations as the innovator product.

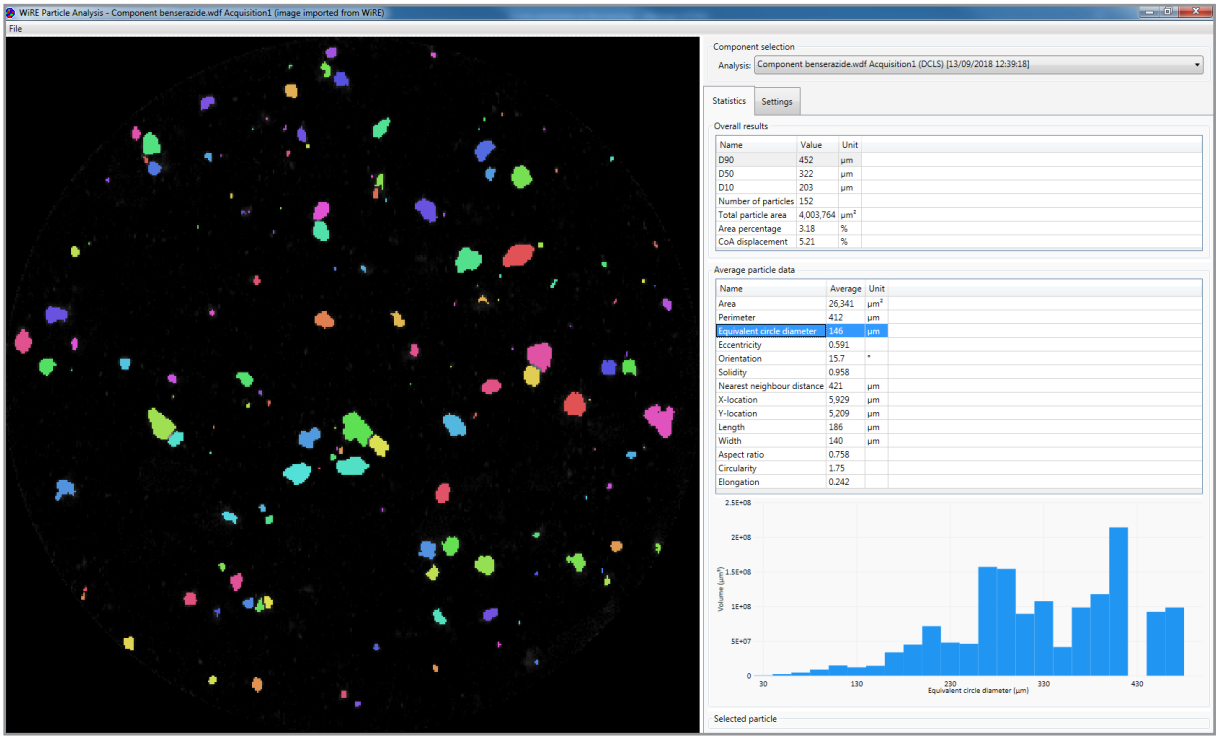
Typically, analysis is performed by quantitative techniques such as HPLC.

Q3 sameness - the final gateway to a biowaiver - has so far been reserved for topical formulations where there is little risk of systemic exposure and, therefore, small changes in delivery profile are unlikely to present patient risk.

Raman imaging

Raman imaging has the power to identify components and quantify amounts which makes it well-suited for identifying Q1 and Q2 sameness.

Q3 sameness - microstructural sameness - is not yet applicable to oral solid dose. However, Raman can quantify the microstructure of solid dose forms, including particle/granule size, uniformity and percentage coverage. Perhaps the demonstration of Q3 sameness using Raman imaging could form one aspect of a series of tests which could pave the way for future biowaivers for oral solid dose?

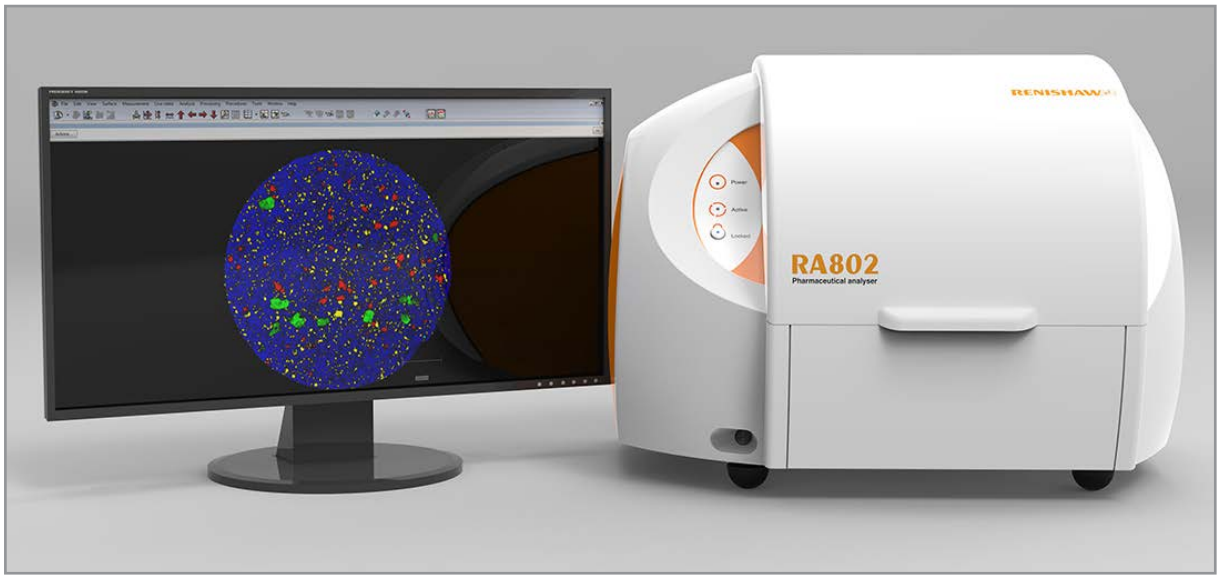


Particle statistics information from Renishaw's WiRE software

In order to determine the microstructure of a formulation, we collect thousands of Raman spectra across the surface of a sample. Each pixel is made up of a complete Raman spectrum and therefore contains all of the chemical information for that sample point.

With Renishaw's StreamLine™ and LiveTrack™ technologies the RA802 Pharmaceutical Analyser can analyse any surface, no matter how rough or smooth, at high speed whilst maintaining image focus. At full speed the system can collect up to 1,500 spectra per second, significantly shortening analysis time compared to conventional Raman systems.

When enough spectra have been collected it is possible to generate a complete chemical image of the sample, including the API, polymorphs, excipients, degradants and contaminants - and segregate all of the requisite components using false colour.



The Renishaw RA802 Pharmaceutical Analyser

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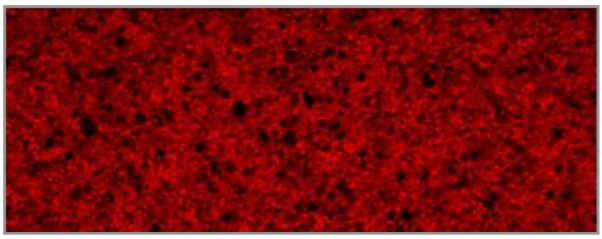
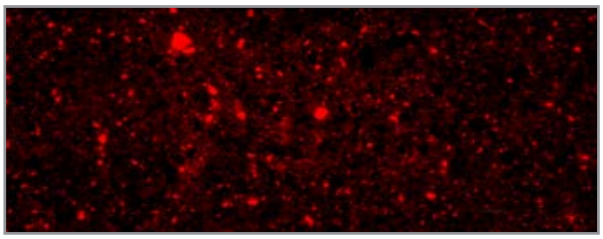
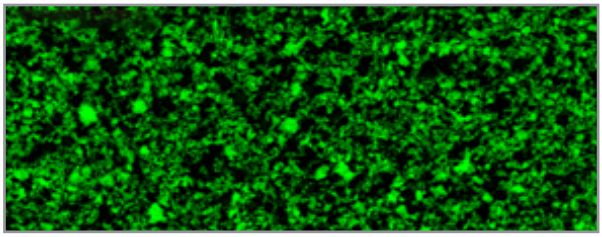
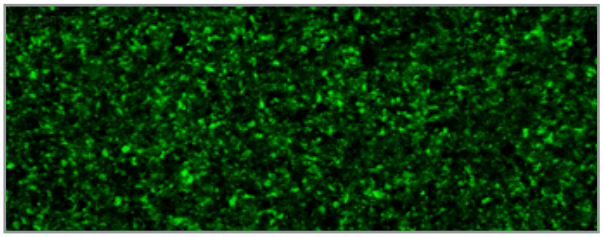
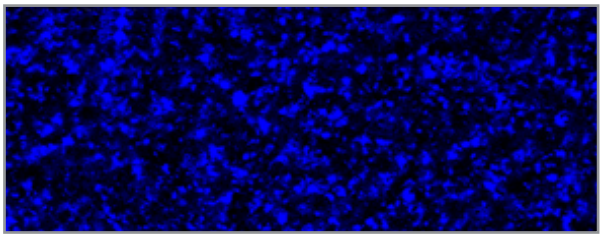
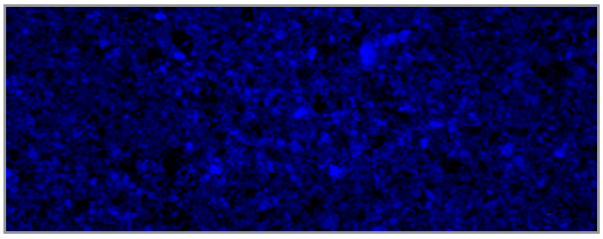
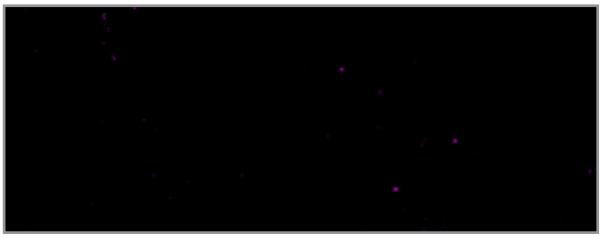
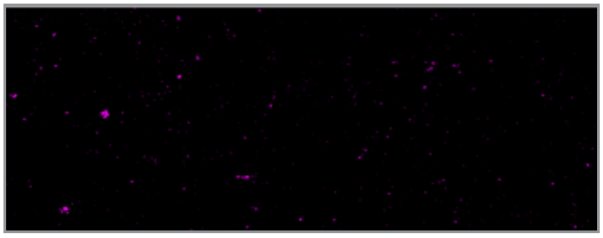
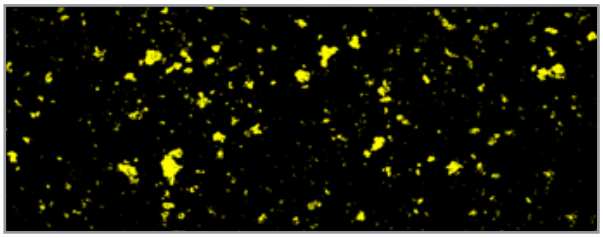
Comparing innovator and generic products

We compared Raman images of two tablets – an innovator and a generic.

The Raman spectra collected were used to identify the different components. The components were false coloured and displayed separately for ease of comparison.

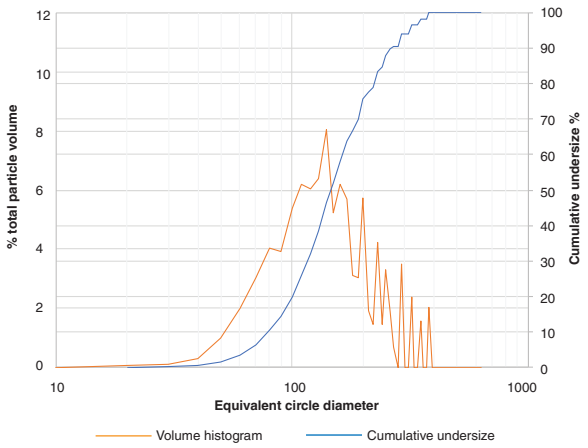
Once each component is identified it is possible to perform particle statistics analysis on the domains and particles within the image. These statistics can be used to compare between tablets, batches and products to identify key differences and diagnose the reasons for those differences.

Innovator	Generic
	
API	*API*
	
Lactose monohydrate	*Lactose monohydrate*
	
Microcrystaline cellulose	*Microcrystaline cellulose*
	
Titanium dioxide (anatase)	*Titanium dioxide (anatase)*
No PVP was found in the innovator product	
PVP	*PVP*

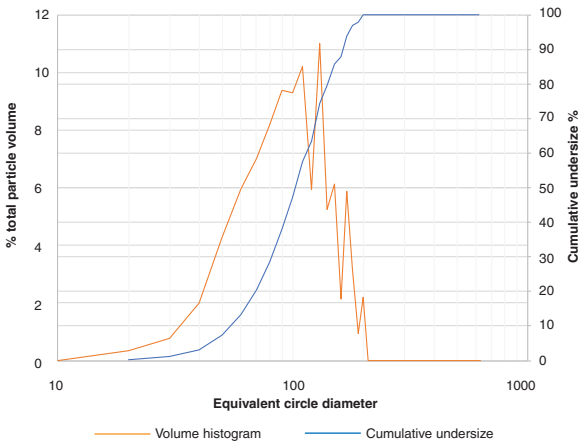
Particle size

Using the data from the Raman images we compared the particle sizes of the microcrystalline cellulose (MCC) and lactose to determine whether there were any significant differences.

Lactose – innovator v generic volume histograms

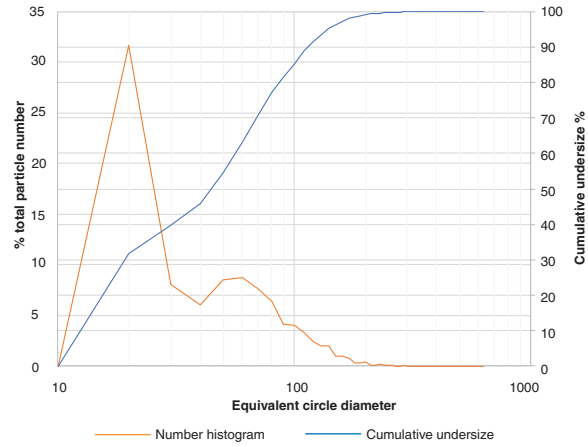


Volume histogram and cumulative undersize of innovator lactose

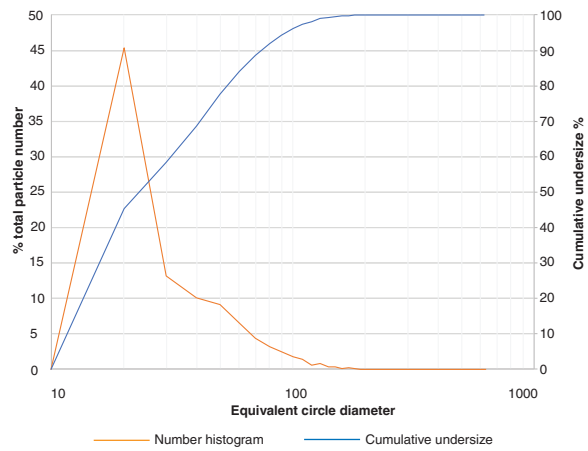


Volume histogram and cumulative undersize of generic lactose

Lactose – innovator v generic number histograms

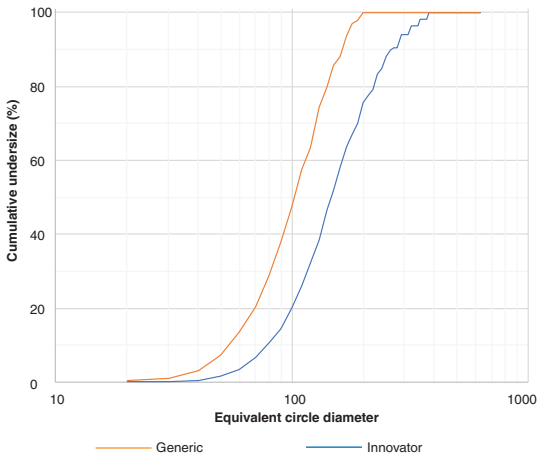


Number histogram and cumulative undersize of innovator lactose

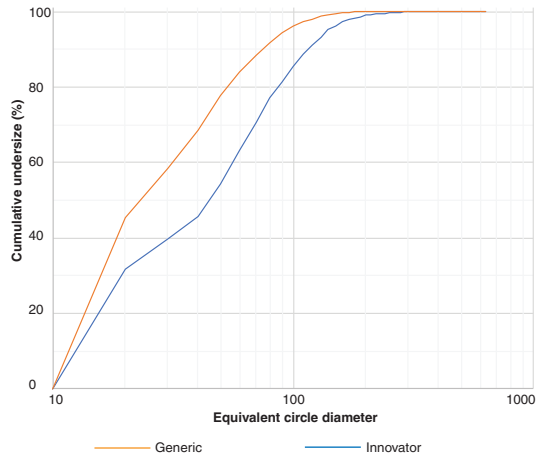


Number histogram and cumulative undersize of generic lactose

Comparison – innovator and generic lactose – cumulative undersize

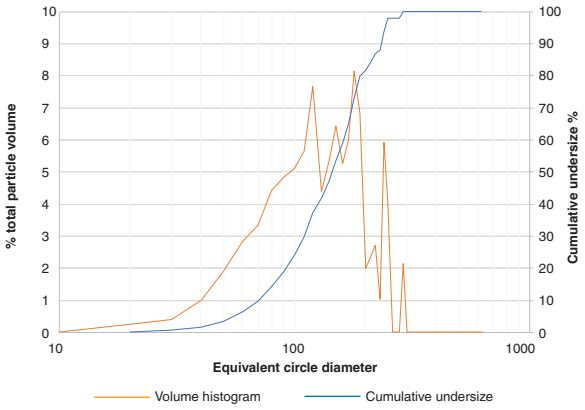


Volume weighted comparison of innovator and generic lactose

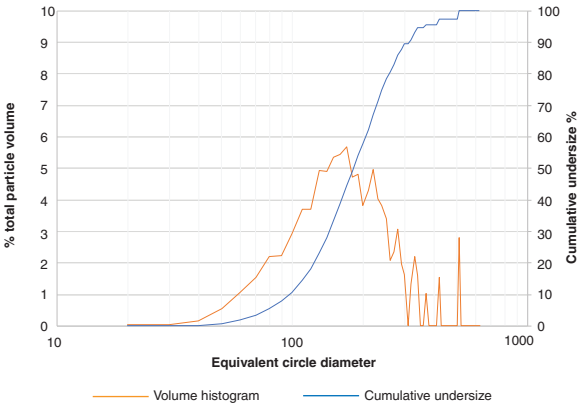


Number weighted comparison of innovator and generic lactose

MCC – innovator v generic volume histograms

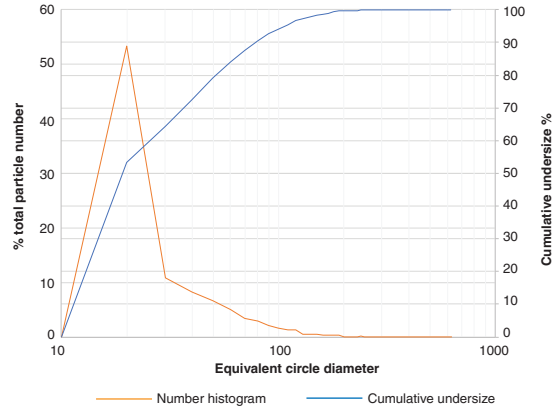


Volume histogram and cumulative undersize of innovator MCC

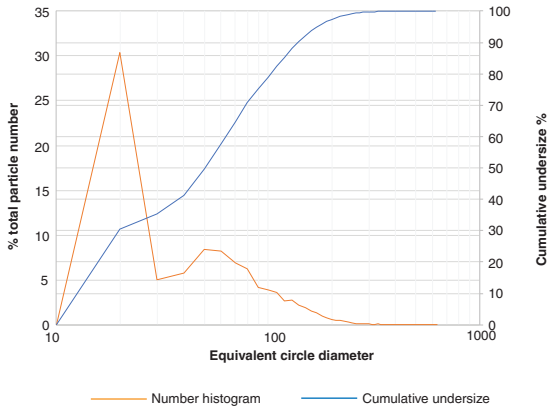


Volume histogram and cumulative undersize of generic MCC

MCC – innovator v generic number histograms

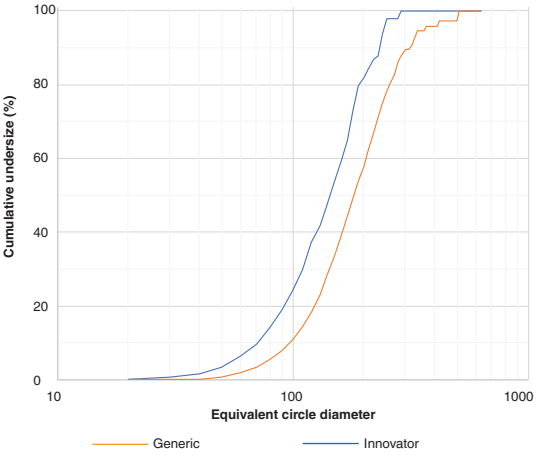


Number histogram and cumulative undersize of innovator MCC

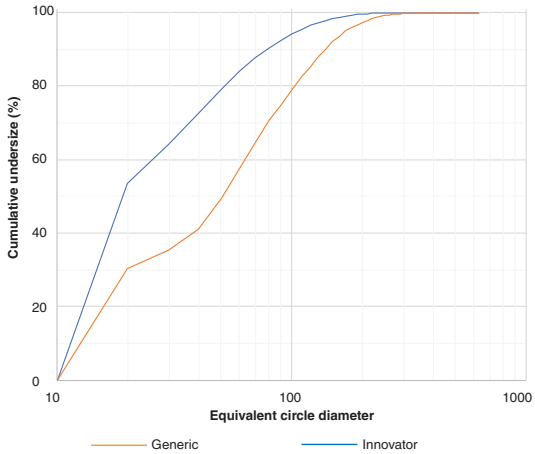


Number histogram and cumulative undersize of generic MCC

Comparison of generic and innovator MCC – cumulative undersize



Volume weighted comparison of innovator and generic MCC



Number weighted comparison of innovator and generic MCC

Comparison of generic and innovator

	Lactose		MCC	
	Generic	Innovator	Generic	Innovator
D90	164 µm	253 µm	298 µm	218 µm
D50	100 µm	142 µm	178 µm	135 µm
D10	49 µm	76 µm	92 µm	63 µm
Number of particles	7385	4702	4614	5936
CoA	1.37%	1.13%	0.18%	3.16%

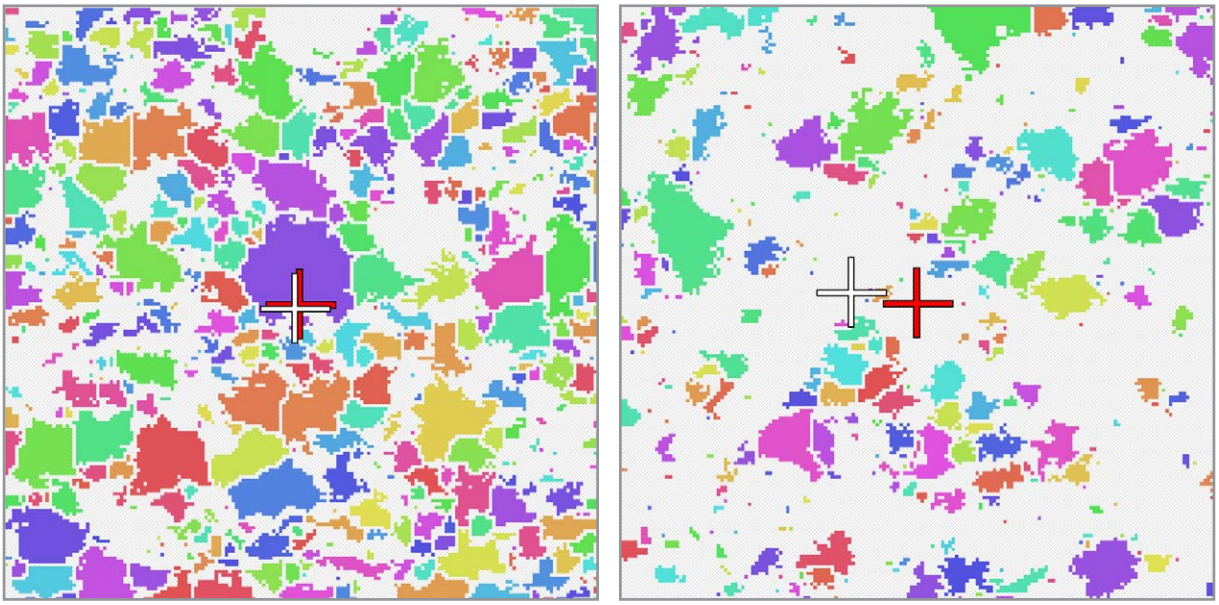
In the case of lactose, the particle size of the generic is consistently smaller than that of the innovator. In the case of the MCC, the particle size of the innovator is smaller than the generic – although the difference is not as stark as that of lactose. The variability in the volume histograms at the higher particle sizes is indicative of a small number of very large aggregates which occupy a large proportion on the total volume.

The graphical data shows that both MCC and the lactose particles in the generic and the innovator products are highly polydisperse; by number, the majority of the particles are between 10 µm – 20 µm (10 µm was the minimum particle size resolution set for this particular sample collection), however, these particles only occupy a fraction of the total volume. The lactose and MCC in the generic and innovator products all have volume-weighted D50 values of between 100 µm – 200 µm.

The number histograms for the innovator lactose and the generic MCC demonstrate some bimodal character – the majority of the particles have a size of 10 µm - 20 µm, however, both graphs exhibit a secondary peak between 50 µm – 60 µm which suggests that the particles may have been sieved to achieve a specific particle size distribution before being added to the tablet blend.

The centre of area (CoA) is used as an indication of a component's uniformity. A 0% CoA indicates that the component of interest is evenly distributed throughout the image such that the centre of area of all the particles is at the centre of the image. Any offset from 0% indicates that the component is not distributed evenly and that a greater proportion of the component is weighted away from the centre.

The CoA for the generic and innovator lactose in the formulations are highly similar. However, there is a marked difference in the CoA of the MCC between the generic and the innovator. It is clear from the images why this may be the case - the generic has a more network-like structure and appears to have much smaller distances between neighbouring particles than the innovator.



Zoomed in extracts from the Centre of Area (CoA) images for the generic (left) and innovator (right) MCC. The red crosses indicate the centre of the image, the white crosses indicate the CoA. A greater offset can be seen in the innovator image.

Discussion

Innovator ingredients	Generic ingredients
API	API
Lactose monohydrate	Lactose monohydrate
Titanium dioxide (anatase)	Titanium dioxide (anatase)
	Polyvinylpyrrolidone (PVP)

The interesting things about these two products is that they are so different from one another.

Even visually, the distribution of the APIs looks completely different. It's an excellent demonstration of the power of Raman imaging – without knowing anything else about the two tablets, it's clear that the two products are being made using very different manufacturing processes.

One wonders about the differences between the mixing and tabletting methods which may have given rise to such differences. The API in the innovator product has a highly dispersed, nebulous structure whereas the API in the generic product forms discreet, aggregated domains. The generic product looks more typical of the types of API distribution that would normally be seen.

Perhaps the innovator product went through a wet granulation step where the API wholly or partially dissolves and then recrystallises – causing it to disperse much more uniformly throughout the formulation.

It is the generic product that really demonstrates the sensitivity of Raman imaging where there exists a mixture of API particles as small as 1 µm as well as large agglomerates. This kind of identification is very difficult using other techniques. It appears the generic tablet has been prepared through simple dry powder compaction as the API is not bound up in granules.

Both tablets contain lactose monohydrate, microcrystalline cellulose and titanium dioxide. RA802 has a spectral database of common excipients and these are easily identifiable.

Interestingly, we also learned that the generic tablet had an additional ingredient contained within it: polyvinylpyrrolidone (PVP).

We found this unusual because we originally believed the generic product was intended to be a direct copy. Possibly this was going into a market where the innovator had not yet been launched, or maybe the plan was to take the product down the 505(b)(2) route.

PVP is a binding agent. It could be the case that the generic polymorph is less 'sticky' and therefore formulators added an additional binding agent to try to improve the tablet's robustness. This is mere speculation.

Although highly unlikely, it might be possible – in some exceptional circumstances – that the FDA would accept an ANDA submission with a differing excipient, provided, however, that the generic company had a sound justification for its inclusion and could conclusively demonstrate the pharmaceutical equivalence to the innovator with regards to dissolution and bioequivalence.

Conclusion

RA802 can be used to successfully characterise innovator and generic products and facilitate deformulation activities.

RA802 can characterise the components, concentrations, particle sizes and distributions of the innovator formulation, allowing generic followers to adjust their processes in order to create equivalent products, or products which are strategically different.

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